Claims 16-17. 45-46, 73-74, 93-94, 103, 113-114, 123, and 133-134 were previously canceled.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-147, and 151-163 are currently under examination.

General Comments

Each of independent claims 1, 30, 58, 86, 106, and 126 has been amended by inserting the word "form" in between "solubility improved" and "has" to improve form. The amendment represents the correction of an obvious typographical error and raises no new issues. Entry of the amendment is accordingly respectfully requested.

In each of independent claims 1, 30, 58 and 86, "eyhyl" has been corrected to "ethyl" in the third to last line as the correction of an obvious typographical error.

Summary of the Rejections

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, and 142-145 continue to be rejected under 35 USC 102(b) over Miyajima, US 4,983,593.

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, and 82-85 continue to be rejected under 35 USC 102(b) as being anticipated by Dunn, US 4,461,759.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 125-127, 132, 135 and 142-145 continue to be rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al., US 5,496,561.

Claims 1, 30, 58, 86, 126, and 156-161 continue to be rejected under §102(e) as anticipated by Bymaster, US 6,147,072.

Claims 146, 147, 151-155, 162, and 163 continue to be rejected under §103(a) as obvious over Bymaster.

Claims 87, 92, 95, 102, 105-107, 112, 115, 122, 124-127, 132, 135, and 142-145 continue to be rejected under §103(a) as obvious over Dunn.

Applicants traverse the rejections for the reasons that follow. References to the Office Action of March 13, 2006 are to the paragraph numbers provided by the Examiner. References to Applicants' specification are to bracketed paragraph numbers in the application published as US 2002/0006443 A1.

The §102 Rejection Over Miyajima

1. Miyajima does not anticipate because it does not disclose a solubility improved drug form. NZ-105, a hydrochloride salt, is excluded from the current claims. It is noted that NZ-105 is also known as efonidipine hydrochloride. NZ-105 was excluded by virtue of the amendments made in Applicants' previous response. The Examiner now contends that NZ-105 is not a simple hydrochloride salt, and that it is a "carboxylate hydrochloride ethanol". Paragraph 2, lines 3-4. The Examiner's contention is apparently that since NZ-105 contains an ethanol solvent molecule, Applicants' did not effectively exclude it.

Miyajima also fails to disclose a composition of HPMCAS and NZ-105 that is a physical mixture, as the claims require.

2. Applicants, in their previous response, specifically excluded hydrochloride salts from their claims. Applicants' claims state that when the drug is basic, the solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form.

3. Applicants traverse the rejection, *inter alia*, on the basis that NZ-105 is a hydrochloride salt which has been excluded from the claims. Salts are defined as substances produced from the reaction between acids, in this case HCl, and bases, in this case the NZ-105 base molecule efonidipine. Grant & Hackh's Chemical Dictionary, Fifth Edition, published by McGraw-Hill, page 516 (copy enclosed). The fact that a hydrochloride salt also contains a solvent molecule is irrelevant. It is still a hydrochloride salt. NZ-105 is, therefore, outside the scope of Applicants' claims.

4. Those skilled in the art readily appreciate that NZ-105 is a hydrochloride salt. In support of this contention, Applicants enclose a copy of "Dissolution Behavior of Efonidipine Hydrochloride" by Okabe et al., Pharmaceutical Sciences, 1995, Vol. 1, Pp 255-258 in which, in the left hand column of page 255 (under "Materials and Methods") the following statement is made:

> The hydrochloride (Fig. 1) is a salt form made by adding hydrochloride and ethanol to efonidipine.

The Examiner's attention is also directed to Figure 1 in which the structure for the ethanolate of efonidipine hydrochloride is illustrated above the legend "Fig. 1. Structural formula of efonidipine hydrochloride".

5. The Examiner's comments in Paragraph 2 that

> Secondly, the proviso does not exclude NZ-105 as drug in a pharmaceutically acceptable form. There is no factual evidence that the NZ-105 would not have at least 2 fold the solubility of the more soluble of the crystalline hydrochloride salt.

are self-contradictory. Applicants excluded crystalline hydrochlorides, including NZ-105. It is inconsistent for the Examiner to implicitly allege that Applicants should demonstrate improved solubility for a compound that is outside the scope of Applicants' claims.

6. Further, Miyajima does not anticipate because Miyajima does not disclose a composition of HPMCAS and NZ-105 that is a physical mixture. Miyajima prepares his compositions by dissolving NZ-105 and HPMCAS in an organic solvent and removing the solvent by evaporation. Miyajima at column 2, lines 37-40. Miyajima's solvent processing method would not produce a physical composition as defined by Applicants, i.e., one in which the individual components retain the same individual physical properties that they exhibit in bulk. See US 2002/0006443-A1 at [0029].

7. For all of the above reasons, it is submitted that Applicants cannot be anticipated by Miyajima, and it is respectfully submitted that the rejection should be withdrawn.

<u>The §102 Rejection Over Dunn</u>

8. Dunn does not anticipate because, *inter alia*, it does not disclose a drug in a solubility-improved form within the scope of Applicants' claims.

9. Both verapamil and verapamil hydrochloride are also outside the scope of Applicants' claims by virtue of the fact that neither has "an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form". The language just quoted excludes the more soluble drug form whether it is the hydrochloride salt or the free base. The remaining form is excluded by virtue of being the less soluble of the two forms. Thus both verapamil and verapamil hydrochloride, i.e., the hydrochloride salt and the free base, are unequivocally excluded.

10. Verapamil and verapamil hydrochloride are the only species disclosed in Dunn within the scope of the phrase "verapamil or a pharmaceutically acceptable salt thereof". No other verapamil species is disclosed. The term "salt form" in Dunn's specification is not a disclosure of a solubility-improved form within the meaning of §102. Dunn discloses nothing else that would constitute a solubility improved form physically mixed with any concentration-enhancing polymer required by Applicants' claims. Thus, the required element of a solubility improved form is missing from Dunn. Because an anticipatory reference must disclose all elements of an invention, Dunn does not anticipate Applicants' claims.

The §102 rejection over Okada

11. Okada does not anticipate because it does not disclose a drug in a solubility-improved form physically mixed with a concentration-enhancing polymer within the scope of Applicants' claims.

12. The Examiner states in Paragraph 7:

> The instant composition comprises a drug and concentration enhancing polymer, where the composition is a dispersion and does not exclude the composition of Okada because Okada does not describe the formation of covalent or ionic bond between the drug and the polymer, such a bond formation would not be a physical process. Also, there is no claim to a physical composition in the examined claims.

Applicants disagree on several grounds.

First, Applicants' composition is not a dispersion. Dispersions are in fact specifically excluded from the claims.

Second, the Examiner appears to be contending that chemical bonds between the drug and polymer must be formed in order to preclude the drug and polymer composition from qualifying as a physical mixture. Applicants respectfully disagree. Considering that an applicant is allowed to be his own lexicographer, a physical mixture is as Applicants defined it in their specification. Applicants defined a physical mixture of a drug and polymer to be, *inter alia*, a composition of drug and polymer that has been physically mixed. That is, some form of mixing action is required to make a mixture. See US 2002/0006443 at [0029] where Applicants indicate that the individual components retain their bulk properties and that any conventional method may be used to mix the polymer and drug together. The dosage form disclosed in Okada, by contrast, is a structure, not a physical mixture. It comprises a polymeric membrane surrounding a central core containing drug, a structure in which no mixing of membrane

components and core components is involved. No embodiment is disclosed in Okada wherein a concentration enhancing polymer required by Applicants is physically mixed with a solubility-improved form of a drug.

Third, Applicants disagree with the Examiner's contention that "...there is no claim to a physical composition in the Examined claims." To the contrary, the claims specifically require that the drug and polymer are combined as a simple physical mixture.

13. Applicants further submit the rejection is legally insufficient to support the rejection. An anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims being rejected. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1349 (Fed. Cir. 1998). Under the authority of cases such as *In re Arkley*, 455 F.2d 586, 587-88 (CCPA 1972), it is impermissible to pick and choose among the hundreds of lines of text in a patent reference in order to arrive at the claimed subject matter. Okada, as stated above does not describe or exemplify any embodiment in which a concentration enhancing polymer required by Applicants is physically mixed with a solubility-improved form of a drug, again noting that a membrane surrounding a drug-containing core is not a "mixture".

14. To base an anticipation rejection on Okada one would need to select a particular polymer from among many polymers in Okada, home in on a particular drug in Okada, and then allege a physical mixture. But, Okada never discloses a physical mixture of one of Applicants' polymers and a solubility-improved drug form. The only disclosure in Okada of any polymer useful in Applicants' invention is in connection with making a membrane, not a physical mixture. The only disclosure of diclofenac sodium (noted by the Examiner in Paragraph 7) is in Example 9 where it is mixed with corn starch, not with a concentration-enhancing polymer. The hydroxypropyl cellulose also mentioned in Example 9 is not one of Applicants' required polymers and Okada clearly applies it as a membrane, not as part of a physical mixture. To repeat, Okada does not disclose a physical mixture of a solubility-improved drug form and a concentration-enhancing polymer. To the extent Okada discloses any elements of Applicants' invention, they are disclosed in isolated and/or unrelated portions of the specification. A §102 rejection cannot be based on Okada by selecting out these isolated elements from the Okada specification and splicing them together, but with no direction in Okada to do so.

The §102 Rejection Over Bymaster

15. Bymaster does not anticipate because it does not disclose a physical mixture of a concentration-enhancing polymer and a solubility improved form of a low-solubility drug.

16. As a preliminary matter, in response to the second sentence in Paragraph 10 of the rejection,

> Bymaster does not describe chemical interaction between the drug and the polymer and the claims do not recite physical interaction or exclude chemical interaction.

Applicants note that the claims specifically require that the solubility improved drug form and the polymer are combined as a simple physical mixture, a term defined in the specification as discussed above. A physical mixture, having been defined as one in which the components retain their physical bulk properties, excludes chemical interaction.

17. The only occurrence in which a polymer required by Applicants' claims is coincidentally disclosed in Bymaster is as an enteric coating. Bymaster, column 10, lines 57-67. A dosage form in which an enteric polymer is coated around a core is not a physical mixture, however, it is a structure. As stated above, physical mixing is required to make a physical mixture. That is the way Applicants defined the phrase "physical mixture", and Applicants' definition excludes coatings because they are not physically mixed. In Bymaster, no mixing of a polymer with a solubility-improved drug form is disclosed otherwise, nor any corresponding physical mixture.

18. Bymaster makes no specific or general disclosure of a solubility-improved form of a drug in combination with a concentration-enhancing polymer, not even when disclosing embodiments of drugs in dosage forms having an enteric polymer coating. Even in the section (column 10, lines 57-67) where Bymaster mentions some of Applicants' polymers for use as enteric coatings, the only specific disclosure of a drug is of duloxetine and of "duloxetine-containing combinations". Duloxetine per se is not a salt, however, much less a solubility-improved drug form. Merck Index, Thirteenth Edition, Published by Merck Research Laboratories, page 611, entry 3498, copy enclosed. In Bymaster's examples, there is no disclosure of any embodiment in which a solubility-improved drug form is physically mixed with a concentration-enhancing polymer required by Applicants' claims.

19. An anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims. I*C.R. Bard, Inc. v. M3 Systems, Inc*, supra. One cannot pick and choose from among unrelated portions of a

disclosure to re-create a claimed invention. *In re Arkley*, supra. Here the Examiner has employed hindsight (i.e., the instant application) to choose a drug, choose a polymer, and then allege a physical mixture. But, such a physical mixture is nowhere disclosed in Bymaster. The anticipation rejection has no legal basis and Applicants accordingly submit that it should be withdrawn.

The §103(a) Obviousness Rejection Over Bymaster

20. Applicants are not obvious over Bymaster because Bymaster does not suggest administering a concentration-enhancing polymer and a solubility improved drug form of a low-solubility drug to a use environment to form a solution.

21. It is well accepted that in order to establish a *prima facie* case of obviousness, an Examiner must satisfy three requirements: (1) there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine reference teachings; (2) the proposed modification of the prior art must have had a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the limitations of the claims. MPEP § 2142. In the instant rejection none of the three requirements has been satisfied.

The first requirement is completely absent as there is no suggestion in Bymaster to administer a concentration-enhancing polymer and a solubility-improved drug form to a use environment. Nor is there any motivation since Bymaster discloses nothing relating to the technical problem of enhancing the concentration of a low-solubility drug. Bymaster does not otherwise disclose any instance in which a solubility-improved drug form and one of Applicants' specifically required concentration-enhancing polymers is administered to a use environment.

The second requirement is missing as well since there is no disclosure in Bymaster proposing any modification of his teachings that would lead one of ordinary skill administer the combination of a concentration-enhancing polymer and a solubility-improved drug form to a use environment.

The third requirement is missing as well, as a consequence of the fact that the first two requirements are missing. With no suggestion or motivation in Bymaster to administer a concentration-enhancing polymer and a solubility-improved drug form to a use environment, and with no suggestion to modify his teachings and/or disclosure, there can be no expectation of success.

22. The rejection can only be based on hindsight. Bymaster is directed to treating psychoses with a combination therapy. Bymaster is totally silent on the problem solved by Applicants, that of increasing the solubility of a sparingly soluble drug. There is thus no motivation in Bymaster to administer a solubility-improved form together with a concentration-enhancing polymer. It is only by picking out unrelated bits of Bymaster's disclosure, a drug here and a polymer there, and then splicing them together with no reason for doing so other than Applicants' specification, that one of ordinary skill in the art might be lead to Applicants' invention. Hindsight is universally rejected as a standard by which to evaluate patentability. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d at 1071, 1075 (Fed. Cir. 1988). Thus, Applicants respectfully submit that Bymaster does not render the claimed invention obvious.

The §103(a) Obviousness Rejection Over Dunn

23. Dunn does disclose granulating, a form of physical mixing also disclosed by Applicants. But Dunn does not disclose granulating a concentration-enhancing polymer with a solubility-improved drug form within the scope of Applicants' claims. The only drugs Dunn discloses within the scope of his claims are verapamil and verapamil hydrochloride, both drugs that are outside the scope of Applicants' claims. Per the requirements for an obviousness rejection as set forth above from MPEP 2142 (1) Dunn is completely silent about the problem of increasing the concentration of a low-solubility drug, (2) there is no disclosure, suggestion or motivation in Dunn which would lead one of ordinary skill to modify Dunn's teachings so as to physically mix a solubility-improved drug form and a concentration-enhancing polymer and (3) Dunn does not teach all elements, namely (a) a physical mixture of (b) a solubility-improved drug form with (c) a concentration-enhancing polymer thereby (d) enhancing drug concentration. Since Dunn lacks any suggestion or motivation to modify his teachings, there can be no reasonable expectation of success.

24. Dunn is in fact concerned with the opposite problem to that solved by Applicants - - controlling the rate of solvation for a drug that is highly or moderately water soluble. Dunn, column 1, lines 18-19. The Dunn formulations retard release rather than enhance concentration. Dunn, column 3, lines 41-49. It is untenable to conclude obviousness from Dunn considering that Dunn is unconcerned with the same technical problem as Applicants, is in fact concerned with the opposite problem, and achieves the opposite result.

Inasmuch as Dunn never discloses or suggests combining any solubility-improved drug form with a concentration-enhancing polymer, Dunn fails to teach or suggest all the limitations of the claims. Accordingly obviousness cannot lie. MPEP § 2142, supra.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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